UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/016,743	01/30/1998	JOSEPH D. ROSENBLATT	176/60192(UR	7389

7590 02/05/2004

MICHAEL L GOLDMAN ESQ
NIXON PEABODY LLP
CLINTON SQUARE
P O BOX 1051
ROCHESTER, NY 14603

EXAMINER	
HELMS, LARRY RONALD	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 20031217

Application Number: 09/016,743
Filing Date: January 30, 1998
Appellant(s): ROSENBLATT ET AL.

Michael Goldman
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 11/4/03.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

NOTE: It is noted that the rejection of claims under 112 second for the tem "capable of binding" has been withdrawn (see Brief pages 14-16).

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The statement is correct.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,824,782	Holzer et al	9/15/95
5,514,554	Bacus	10/7/93

Huston et al., Meth. Enzymol. 203:46-88, 1991

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The rejection under 35 U.S.C. 103(a) is reiterated for convenience:

Claims 1, 3-8, 10, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holzer et al (U.S. Patent 5,824,782, filed 9/15/95) and further in view of Huston et al (Meth. Enzymol. 203:46-88, 1991).

Holzer et al teach a fusion protein comprising an antibody to the EGF receptor, which is a tumor cell surface antigen expressed on breast cancer cells, (see abstract and column 1, lines 1-15) and the chemokine IL-8 that retains its activity (see column 6, lines 52-59). The construct comprises the antibody and a linker connecting the domains (see column 4, lines 55-56) and compositions of the chimeric molecules in PBS (see column 5, line 25, and column 8, lines 49-50). Holzer et al also teach the chemokine RANTES (see column 2, lines 37-40). The recitation of the intended use of "stimulating

a tumor specific immuno response" is given no patentable weight in this rejection. Holzer et al does not teach a fusion protein comprising the chemokine linked to the N terminus of the antibody. This deficiency is made up for in the teachings of Huston et al.

Huston et al teach Fusion proteins with the effector fused at the amino terminal of the heavy chain of the antibody (see pages 55-59 and Figure 3A).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have made a construct comprising a binding domain which specifically binds to a tumor cell associated antigen and a chemokine fusion as taught by Holzer et al with the chemokine linked to the amino terminus of the heavy chain as taught by Huston et al.

One of ordinary skill in the art would have been motivated to produce the claimed invention because Holzer et al teach "new fusion proteins which consist of a tumor-associated targeting element, preferably a monoclonal antibody or a fragment thereof, recognizing and specific for a molecule which is preferentially expressed on tumor cells... and a biologically active ligand selected from the group of chemokine proteins....can be used in tumor therapy and diagnostics." (See column 1, lines 1-15). In addition, one of ordinary skill in the art would have been motivated to produce the claimed invention because Huston et al teach "sFv analogs suggested that VL or VH domain, respectively in each orientation, would tolerate amino-terminal fusion" (see page 57, first full paragraph).

Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because Holzer et al teach "fusion proteins according to the invention... could in fact cause chemotactic activity" (see column 7, lines 13-16). In addition, one of ordinary skill in the art would have had a reasonable expectation of success because Huston et al teach "Investigations have demonstrated that protein effector domains can be successfully fused to the amino terminus of the sFv." (See page 57, second full paragraph).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Response to Arguments

Appellants state on pages 7-8 of the Brief descriptions of Holzer and Huston as they interpret the art. The Brief states that Holzer discloses immunoconjugates comprising an antibody or fragments and a cytokine. Holzer teach the chemokine is preferably selected from C-X-C family such as IL-8 and the N-terminus of IL-8 is conjugated to the carboxy terminus of the Fab fragment of the antibody. In response to these statements, Holzer et al also teach the chemokine RANTES (see column 2, lines 37-40) in addition to the preferred embodiment of C-X-C chemokines. Holzer also teach that the chemokine can be conjugated to the C-terminus of a Fv fragment or an antibody(see Figure 1).

The Brief then has a description of what Huston teaches (see page 8 of the Brief). Appellants state that Huston relates to single chain Fv analogs and fusion

proteins and the single-chain Fv consists of VH non-covalently associated with a VL and then state that the VH and VL have a linker. In response to this a single chain antibody is a VH-VL or VL-VH with a linker covalently associating the VH and VL domains. Appellants state that single-chain Fv lack the constant regions of the native IgG and the conformation of such. In response to this, while the structure of a single chain Fv is different from an IgG with the constant region, single chain molecules have binding sites that like antibodies retain binding to an antigen as demonstrated in Huston.

On page 8-12 of the Brief Appellant argue the combination of Holzer and Huston would not have rendered the claimed invention obvious. Appellants argue that Holzer's immunoconjugates bind the N-terminal of IL-8 to the carboxy terminus of the Fab fragment, thus, Holzer does not satisfy the requirement that the chemokine be "coupled to the N-terminus of the heavy or light chain of the antibody". Appellants state that The portion of Huston relied on is single chain constructs and these are molecules that are VH and VL domains connected with a linker and native IgG molecules contain the VH, VL and constant regions, CH1, CH2, CH3, thus, single chain molecules lack constant regions.

In response to this argument, the rejection is based on a combination of references and as was stated in the rejection Holzer does not teach a chemokine coupled to the N-terminus of a light or heavy chain. The arguments above with regard to Huston does not add anything to the argument, except pointing out differences in domains between single chain and IgG antibodies.

Appellants argue that as demonstrated in the Declaration of Seung-Uon Shih that one of ordinary skill in the art would have no basis to adapt the teachings of Huston regarding single chain FV analogs to whole antibodies immunoconjugates of Holzer (see page 9 of the Brief). Appellants argue that the declaration demonstrates that there are significant differences with regard to avidity, half life, and chemokine carriage which would cause scientist skilled in the field of antibody cancer therapeutics to avoid adapting single chain Fv analog technology to whole antibody cancer therapeutics. The Brief then addresses each of these areas (see pages 10-11). Applicants state that the declaration demonstrates that whole antibodies have two binding sites and single chains have one and whole antibodies have stronger binding (avidity) and half life of whole antibodies is generally longer and whole antibodies carry two molecules of chemokine but single chain Fv analogs carry only single chemokines and thus an antibody carrying two chemokine molecules would tend to be more efficient at signaling (see page 10-11 of Brief). The Brief then addresses the response of the Examiner to the Declaration and states that the argument overlooks points made in the Shin Declaration that one would not adapt single chain antibody technology to whole antibodies because of the differences.

In response to these arguments, The declaration and arguments presented in the Brief have been carefully considered but are deemed not to be persuasive. Again the examiner acknowledges that there are differences between single chain antibodies and whole antibodies as defined by having VH, VL, constant regions of CH1, CH2, CH3. While there are differences, one does not have to adapt the teaching of single chain

antibodies to whole antibodies. The prior art of Holzer teaches conjugation to both single chain and whole antibodies. Holzer teach both single chain antibodies and whole antibodies (see Figure 1, mAb425-CH3-CHEMOKINE and mAb425-Fv-CHEMOKINE) that have a chemokine at the C-terminal, mAb425-CH3-CHEMOKINE has the chemokine at the C-terminal of both the CH3 domains and the mAb425-Fv-CHEMOKINE has the chemokine at the C-terminus of the VH domain. Therefore both whole and single chain molecules have been shown to have the chemokine conjugated and still retain binding to antigen and have chemokine activity. While the Declaration of Shin does demonstrate differences between the whole and single chain molecules, the declaration could actually be used to demonstrate why one skill in the art would prefer to have whole antibodies and provide motivation for using whole antibodies, however, the issue at hand is not whether one needs to adapt whole antibody technology to single chain technology it is whether one skill in the art would adapt a chemokine to the C-terminus to conjugating a chemokine to the N-terminus of a heavy or light chain. Clearly Holzer teach that the constructs of mAb425-CH3-CHEMOKINE and mAb425-Fv-CHEMOKINE both bind EGFR and IL-8, thus the antigen binding site and the chemokine binding site are active and capable of binding. In addition, Holzer clearly shows two chemokines conjugated in whole antibodies or antibodies with two binding sites and therefore one would want not have to adapt the whole antibody technology to single chain technology to conjugate two chemokines as discussed in the Declaration of Shin. The mAb425-Fv-CHEMOKINE comprises a single chain antigen binding site of the antibody which when conjugated to the chemokine retains binding to the antigen.

This is important in view of the teachings of Huston. Huston teaches that single chain Fv fusion proteins can involve two schemes where an effector can be fused at the amino terminus of an Fv or at its carboxyl terminus and since constant domains are always attached to the C termini of the V region in the immunoglobulin superfamily, there is ample precedent for using this orientation. Huston also teach that "early development of VH-VL or VL-VH sFv analogs suggested that the VL or VH domain, respectively in each orientation, would tolerate amino-terminal fusion of the linker without significant impact on antigen binding site properties" and "Investigations have demonstrated that protein effector domains can be successfully fused to the amino terminus of the sFv" and cites numerous examples (see page 55-57). Thus, Huston teach that the antigen binding site is not altered in the conjugation of the effector to the N-terminus. This is important in the context of Holzer because Holzer also teach that conjugation in the Fv did not result in alteration in either antigen binding or effector function, IL-8 activity. Therefore, since the single chain has a VL and VH and mimics the antigen binding site in whole antibodies, albeit, one binding site, and the binding site is still capable of binding antigen with either the effector at the C-terminus (as taught by Holzer and Huston) or N-terminus (as taught by Huston) it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to conjugate the chemokine to the N-terminus of the heavy or light chain of an antibody.

The rejection under 35 U.S.C. 103(a) is reiterated for convenience:

Claims 1 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huston et al (Meth. Enzymol. 203:46-88, 1991), and further in view of Bacus (U.S. Patent 5,514,554, filed 10/7/93) and Holzer et al (U. S. Patent 5,824,728, filed 9/15/95).

Huston et al and Holzer have been described supra. Huston et al does not teach a binding domain specific for her2/neu. This deficiency is made up for in the teachings of Bacus.

Bacus teach monoclonal antibodies to her2/neu.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have made a construct comprising a binding domain which specifically binds her2/neu as taught by Bacus and a chemokine as taught by Holzer et al and couple the chemokine and the antibody by the N terminus as taught by Huston et al.

One of ordinary skill in the art would have been motivated to produce the claimed invention because Holzer et al teach "new fusion proteins which consist of a tumor-associated targeting element, preferably a monoclonal antibody or a fragment thereof, recognizing and specific for a molecule which is preferentially expressed on tumor cells... and a biologically active ligand selected from the group of chemokine proteins....can be used in tumor therapy and diagnostics." (See column 1, lines 1-15). In addition, one of ordinary skill in the art would have been motivated to produce the claimed invention because Bacus teach the antibodies to her2/neu can be used alone or linked to conjugates which can be used as therapeutic agents (see column 4, lines 10-15). In addition, one of ordinary skill in the art would have been motivated to

produce the claimed invention because Huston et al teach "sFv analogs suggested that VL or VH domain, respectively in each orientation, would tolerate amino-terminal fusion" (see page 57, first full paragraph).

Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because Holzer et al teach "fusion proteins according to the invention... could in fact cause chemotactic activity" (see column 7, lines 13-16). In addition, one of ordinary skill in the art would have had a reasonable expectation of success because Bacus teach the antibodies of the present invention are specific for the her2/neu product and significantly inhibit the tumorigenic growth of her2 cells. (See column 3, lines 59-67). In addition, one of ordinary skill in the art would have had a reasonable expectation of success because Huston et al teach "Investigations have demonstrated that protein effector domains can be successfully fused to the amino terminus of the sFv." (See page 57, second full paragraph).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Response to Arguments

Appellants state on page 13 of the Brief that The combination of Huston, Bacus, and Holzer would not have rendered the claimed invention obvious. Appellants states that one of ordinary skill in the art would have no basis to adapt the teachings of Huston regarding single chain Fv analogs to the whole antibody immunoconjugates of

Holzer, for all the reasons set forth supra and Bacus does not overcome the above-noted deficiencies of Huston and Holzer.

In response to this argument, the references of Holzer and Huston have been addressed supra and Bacus does not have to overcome any deficiencies except for providing monoclonal antibodies to her2/neu and motivation to use such which was provided in the rejection.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The rejection under 35 U.S.C. 112, second paragraph is reiterated for convenience:

Claims 1, 3-10, 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3-10, 25 are indefinite for reciting "complete antibody" in claim 1 because the exact meaning of the phrase is not clear. Does the phrase mean "complete" in the sense of binding or having the function of the antibody such as binding or Fc mediated function, or does the antibody comprise a constant region of CH1, CH2, and CH3?

Response to Arguments

Appellants state on page 14 of the Brief that the phrase "complete antibody" in not indefinite. Appellants state that the term "antibody" as used in the present application is defined at page 22, line 31 to page 23, line 4 and the term refers to various types of immunoglobulins, including IgG, IgM, and IgA, and their relative subclasses and also include antibody fragments such as , for example, Fab, Fab')2 and Fv fragments, and the corresponding fragments obtained from antibodies other than IgG and since the term "antibodies" is defined as including whole antibodies like IgG, IgM, and IgA, as well as fragments, it is apparent that the phrase "complete antibody" means complete in the sense of having a complete structure, i.e. an antibody structure having VH and VL domains as well as constant regions CH1, CH2, and CH3 and Huston teach such in Figure 1A.

In response to this argument, as admitted to the phrase "antibodies" refers to "whole antibodies" as well as fragments, therefore does the term mean in the context of "complete antibody". The phrase is not defined in the specification. In addition, what is the difference between the phrase "complete antibodies" and "whole antibodies" and is there a difference. While Huston has an IgG antibody in Figure 1A, the specification does not define what a "complete antibody" is and as such does it only have a VH and VL or does it have additional domains or does "complete" mean antigen binding or having the function of the antibody such as binding or Fc mediated function?

The rejection under 35 U.S.C. 112, first paragraph is reiterated for convenience:

Claims 1, 3-10, and 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 has been amended to recite "a complete antibody". Support for the claim was not described in the response filed 7/19/02. The specification does not describe a "complete antibody". The specification discloses antibodies as various types including IgG and may be monoclonal or polyclonal and be of any species origin and chimeric and include fragments (see pages 22-23). Applicant is required to provide specific support for the claimed limitation in the specification as originally filed or remove it from the claims.

Response to Arguments

Applicants argue on page 16 of the Brief that The rejection of claims 1, 3-10, and 25 for lack of descriptive support is improper. Appellants state that the present application describes chimeric molecules having a complete or fully assembled H2L2 form and Figure 2, 3, and 10 of the present application shows complete antibody structure and one skill in the art would know a complete antibody means VH, VL, CH1, CH2, and CH3 and this is shown in Huston Figure 1A.

In response to this argument, while Huston teaches an IgG antibody, the specification does not describe what a "complete antibody" is (see 112 second above)

and as such the specification does not support the phrase "complete antibody". While the specification teaches RANTES.Her2.IgG3 and B7.her2.IgG3 and a complete H2L2 form was secreted, it is still not clear where support for the phrase can be found because again the phrase encompasses many forms of the antibody molecule.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

LARRY R. HELMS, PH.D
PRIMARY EXAMINER

Larry R. Helms
December 18, 2003

Conferees
Anthony Caputa AU 1642
Yvonne Eyler AU 1646

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER Conferee
TECHNOLOGY CENTER 1600

MICHAEL L GOLDMAN ESQ
NIXON PEABODY LLP
CLINTON SQUARE
P O BOX 1051
ROCHESTER, NY 14603

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600